ORGANIC LETTERS

2001
Vol. 3, No. 22
3549−3552

Synthetic Studies toward Gambierol. Convergent Synthesis of the Octacyclic Polyether Core

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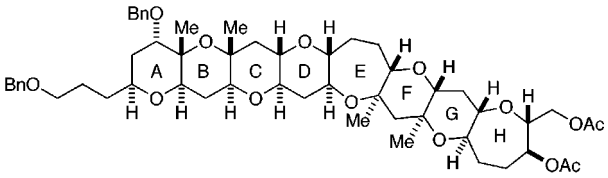
Received August 28, 2001

ABSTRACT



A convergent synthetic route to the octacyclic polyether core of gambierol, a marine polycyclic ether toxin, has been developed. The synthesis involves construction of two fragments representing the ABC and EFGH ring systems followed by their coupling via a *B*-alkyl Suzuki reaction.

The fused polyether class of marine natural products, exemplified by brevetoxins, ciguatoxins, and maitotoxin, has received much attention due to the biological potency and structural complexity of these molecules.[1,2] Gambierol (**1**) was isolated as a toxic constituent from cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus* and exhibits mouse lethality with an LD_{50} value of 50 μg/kg (ip).[3] The symptoms caused in mice resemble those shown for the ciguatoxins, which are the principal toxins responsible for ciguatera fish poisoning, implying the possibility that gambierol is also implicated in ciguatera. The biological basis of the toxicity, however, remains unknown, mainly due to an extremely limited availability. The gross structure, including relative stereochemistry, has been determined by Yasumoto and co-workers on the basis of extensive NMR analysis.[3] Recently, the absolute configuration has been unambiguously established by application of a chiral anisotropic reagent.[4] Its characteristic polyether structure and potent biological activity, as well as the scarcity from natural sources, make gambierol an intriguing synthetic target molecule.[5] In the course of our studies toward the total synthesis of gambierol (**1**), we have reported the convergent

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(1) For recent reviews on marine polycyclic ether toxins, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897−1909. (b) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3−18. (c) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, 293−314. (d) Yasumoto, T. *Chem. Rec.* **2001**, *3*, 228−242.

(2) For recent reviews on polyether synthesis, see: (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953−1980. (b) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849−852.

(3) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361−362.

(4) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 97−100.

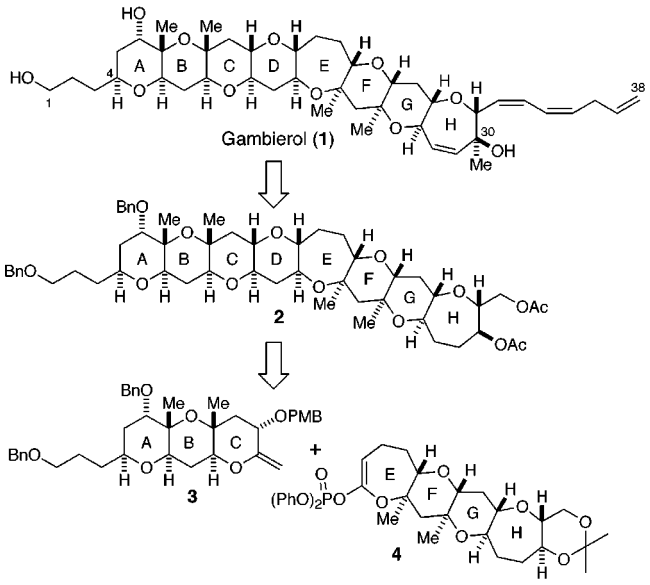
(5) (a) Kadota, I.; Park, C.-H.; Ohtaka, M.; Oguro, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6365−6368. (b) Kadota, I.; Kadowaki, C.; Yoshida, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6369−6372. (c) Kadota, I.; Ohno, A.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 6373−6376. (d) Kadowaki, C.; Chan, P. W. H.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 5769−5772. (e) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 6702−6703. (f) Kadota, I.; Takamura, H.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 4729−4731. (g) Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749−2752. (h) Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919−2922. (i) Kadota, I.; Park, C.-H.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6195−6198. (j) Kadota, I.; Kadowaki, C.; Takamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6199−6202.

10.1021/ol0166597 CCC: $20.00
Published on Web 10/10/2001

synthesis of the EFGH ring system.[6] Herein we describe the synthesis of the ABC ring system and its union with the EFGH ring system via the *B*-alkyl Suzuki coupling-based strategy,[7−9] leading to the octacyclic polyether core **2** of gambierol.

We envisioned that the polyether core of gambierol (**1**) could be constructed by hydroboration−Suzuki cross-coupling of two fragments representing the ABC and EFGH ring systems (**3** and **4**,[6] respectively) (Scheme 1). With the

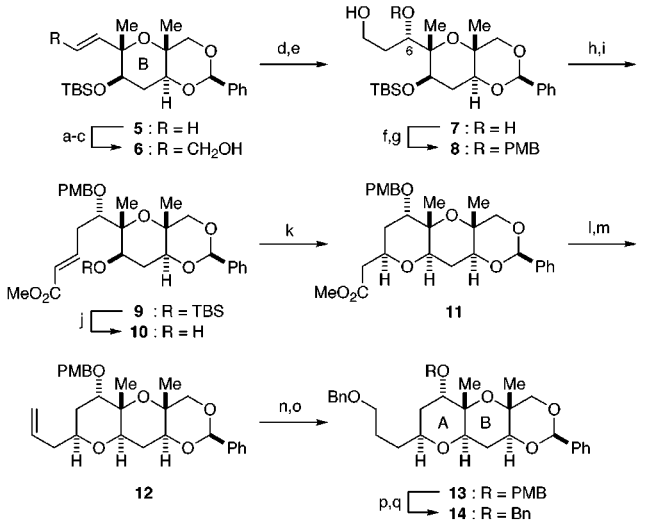
Scheme 1. Structure and Retrosynthetic Analysis of Gambierol (**1**)



polyether core in hand, functionalization of the H ring and installation of the triene side chain would complete the total synthesis of **1**.

Synthesis of the ABC ring *exo*-olefin **3** started with the known compound **5**[10] and followed substantial literature precedent[5a] (Scheme 2). Oxidative cleavage of the double

Scheme 2[a]



[a] Reagents and conditions: (a) OsO_4, NMO, THF−H_2O; then $NaIO_4$; (b) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, *t*-BuOK, THF, −78 → 0 °C; (c) DIBALH, CH_2Cl_2, −78 °C, 85% (four steps); (d) *t*-BuOOH, $Ti(Oi\text{-Pr})_4$, (−)-DET, 4 Å molecular sieves, CH_2Cl_2, −20 °C; (e) Red-Al, THF, −40 → 0 °C, quantitative (two steps); (f) *p*-$MeOC_6H_4CH(OMe)_2$, PPTS, CH_2Cl_2, rt; (g) DIBALH, CH_2Cl_2, −40 → 0 °C, 80% (two steps); (h) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (i) $Ph_3P{=}CHCO_2Me$, toluene, 80 °C, quantitative (two steps); (j) TBAF−HOAc (1:1), THF, rt → 35 °C, 1.5 days, 91%; (k) NaH, THF, rt, 86%; (l) DIBALH, CH_2Cl_2, −78 °C; (m) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 91% (two steps); (n) 9-BBN, THF, rt; then aqueous $NaHCO_3$, H_2O_2; (o) *t*-BuOK, BnBr, THF, TBAI, rt, 93% (two steps); (p) DDQ, pH 7 buffer−CH_2Cl_2, rt; (q) *t*-BuOK, BnBr, TBAI, THF, rt, 93% (two steps).

bond followed by Horner−Emmons reaction and DIBALH reduction gave allylic alcohol **6** (Scheme 2). The C6 hydroxyl group[11] was installed by Sharpless asymmetric epoxidation and subsequent reduction with Red-Al[12] to afford 1,3-diol **7** as the sole product. Diol **7** was converted to an anisilidene derivative, which was treated with DIBALH to induce regioselective reductive opening to give primary alcohol **8**. Oxidation to the aldehyde followed by Wittig elongation gave α,β-unsaturated ester **9**. After removal of the TBS group, treatment of the derived alcohol **10** with NaH in THF induced hetero-Michael reaction to afford ester **11** in 86% yield. DIBALH reduction and Wittig methylenation of the derived aldehyde gave terminal olefin **12**, which upon hydroboration−oxidation and protection provided benzyl ether **13**. The PMB group was then replaced with the benzyl group to give **14**.

(6) (a) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371−8375. (b) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019−3033.

(7) (a) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027−9030. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075−1077. (c) Sasaki, M.; Noguchi, K.; Fuwa, H.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 1425−1428. (d) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1090−1093.

(8) The *B*-alkyl Suzuki coupling has been successfully used in natural product syntheses, see: (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015. (b) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem. Soc.* **1996**, *118*, 8250−8257. (c) Narukawa, Y.; Nishi, K.; Onoue, H. *Tetrahedron* **1997**, *53*, 539−556. (d) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818−6819. (e) Balog, A.; Harris, C.; Savin, K.; Zhang, K.-G.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2675−2678. (f) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885−7892. (g) Fürstner, A.; Konetzki, I. *J. Org. Chem.* **1998**, *63*, 3072−3080. (h) Meng, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1485−1488. (i) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542−3545. (j) Zhu, B.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2575−2578. (k) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687−2690. (l) Chelmer, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695−2698. (m) Lee, C. B.; Chou, T.-C.; Zhang, X.-G.; Wang, Z.-G.; Kuduk, S. D.; Chappell, M. D.; Stachel, S. J.; Danishefsky, S. J. *J. Org. Chem.* **2000**, *65*, 6525−6533 and references therein.

(9) For reviews on Suzuki cross-coupling reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

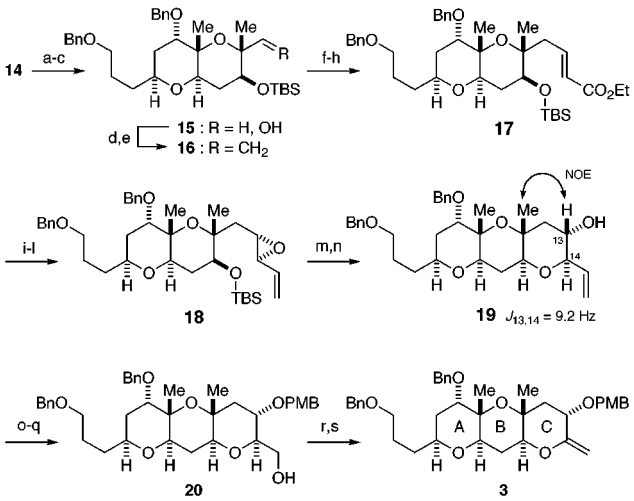
(10) Compound **5** is available in 12 steps from 2-deoxy-D-ribose, see: Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517−4552.

(11) The numbering of carbon atoms of all compounds in this paper corresponds to that of gambierol.

(12) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719−2722.

The synthesis of the C ring was envisioned to occur via acid-catalyzed ring opening of hydroxy epoxide (Scheme 3).[13] Toward this end, **14** was converted to alcohol **15** in a

Scheme 3[a]

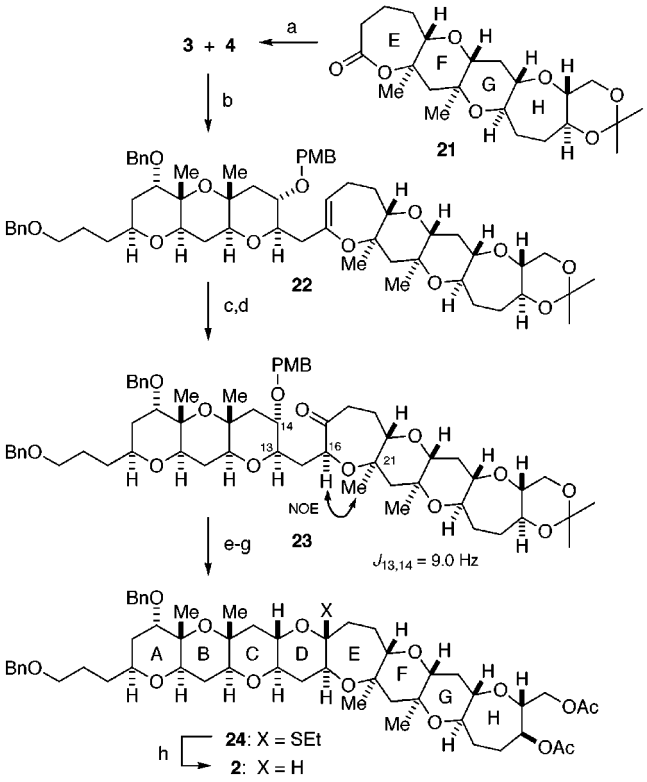


[a] Reagents and conditions: (a) *p*-TsOH·H_2O, MeOH, rt; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) CSA, MeOH, rt, 86% (three steps); (d) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 95%; (e) Tebbe reagent, THF, 0 °C, 96%; (f) 9-BBN, THF, rt; then aqueous $NaHCO_3$, H_2O_2; (g) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (h) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, *t*-BuOK, THF, −78 → 0 °C, 90% (three steps); (i) DIBALH, CH_2Cl_2, −78 °C, 99%; (j) *t*-BuOOH, $Ti(O\text{-}i\text{-Pr})_4$, (+)-DET, 4 Å molecular sieves, CH_2Cl_2, −28 °C, 92%; (k) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (l) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 90% (6:1, two steps); (m) TBAF, THF, rt, 96%; (n) PPTS, CH_2Cl_2, rt, 79%; (o) *t*-BuOK, PMBCl, TBAI, THF, rt; (p) OsO_4, NMO, THF−H_2O; then $NaIO_4$, rt; (q) $NaBH_4$, MeOH, 0 °C → rt, 86% (two steps); (r) I_2, PPh_3, imidazole, benzene, rt; (s) *t*-BuOK, THF, 0 °C, 86% (two steps).

conventional three-step sequence. Oxidation of **15** followed by treatment of the derived aldehyde with Tebbe reagent[14] gave olefin **16**,[15] which was then converted into α,β-unsaturated ester **17** in a three-step sequence as shown. DIBALH reduction, asymmetric epoxidation, oxidation, and Wittig reaction produced vinyl epoxide **18** as an inseparable 6:1 mixture of diastereomers. After desilylation, cyclization of the resultant epoxy alcohol with PPTS afforded a mixture of the desired tricyclic **19** and its diastereomer, which was readily separated by silica gel chromatography. The structure of **19** was confirmed by coupling constant, $J_{13,14} = 9.2$ Hz, and NOE experiments as shown. Protection as the PMB ether was followed by oxidative cleavage of the double bond and subsequent reduction of the derived aldehyde with $NaBH_4$ to give alcohol **20**, which was then converted to the desired *exo*-olefin **3** without incident.

With the ABC ring **3** in hand, the crucial coupling reaction with enol phosphate **4** was next attempted (Scheme 4). The

Scheme 4[a]



[a] Reagents and conditions: (a) KHMDS (3 equiv), $(PhO)_2P(O)Cl$ (10 equiv), THF−HMPA (10:1), −78 °C, quantitative; (b) **3**, 9-BBN, THF, rt; then 3 M aqueous Cs_2CO_3, **4**, $PdCl_2(dppf)\cdot CH_2Cl_2$, DMF, 50 °C, 22 h, 86%; (c) BH_3·THF, THF, 0 °C → rt; then 3 M aqueous NaOH, H_2O_2, rt, 87%; (d) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 98%; (e) DDQ, pH 7 buffer−CH_2Cl_2, rt; (f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt; (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 75% (three steps); (h) Ph_3SnH, AIBN, toluene, 110 °C, 95%.

requisite **4** was prepared from the precursor lactone **21**[6b] by treatment with KHMDS and $(PhO)_2P(O)Cl$ in THF−HMPA (10:1, 10 mM) at −78 °C. Hydroboration of **3** with 9-BBN-H[16] and subjection of the resultant alkylborane to **4** under the previously reported conditions using aqueous 3 M Cs_2CO_3 and $PdCl_2(dppf)\cdot CH_2Cl_2$ (50 mol %) in DMF at 50 °C for 22 h[6,8b] furnished the desired cross-coupled product **22** in excellent yield. Subsequent hydroboration with BH_3·THF (THF, 0 °C → rt) proceeded stereoselectively to give, after oxidative workup, an alcohol (87%), which was then oxidized with TPAP/NMO[17] to afford ketone **23** in 98% yield.[18] The stereochemistry of **23** was unambiguously determined by the large coupling constant, $J_{13,14} = 9.0$ Hz, and NOE between 16-H and 24-Me as shown. Oxidative removal of the PMB group provided the corresponding hemiketal, which upon exposure to EtSH and $Zn(OTf)_2$ effected formation of the mixed thioketal with concomitant

(13) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330−5334.

(14) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613.

(15) Wittig methylenation of the aldehyde resulted in a low yield (26%) of **16**.

(16) 9-BBN-H dimer was recrystallized from anhydrous dimethoxyethane prior to use.

(17) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(18) Stereochemistry of the alcohol was not determined. So, we cannot exclude a possibility that exclusive formation of ketone **23** results from an equilibration reaction after oxidation with TPAP/NMO.

loss of the acetonide group. Subsequent acylation provided diacetate **24** in 75% yield over three steps. Finally, radical reduction[7d,19] proceeded cleanly to furnish the octacyclic polyether core **2** of gambierol (**1**) in 95% yield.

In conclusion, the first synthesis of the octacyclic polyether core of gambierol (**1**) has been achieved in a convergent manner. The present synthesis has demonstrated the generality of our *B*-alkyl Suzuki coupling-based approach for the convergent assembly of a fused polyether structure. Further studies toward the total synthesis of gambierol (**1**) are currently underway and will be reported in due course.

Acknowledgment. A fellowship (to H.F.) from the Japan Society for the Promotion of Science is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0166597

(19) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc*. **1989**, *111*, 5321−5330.